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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/407,660	09/28/99	LANDER E	WHIFG98-16PA

EXAMINER

JOHANNSEN, D

ART UNIT	PAPER NUMBER
1655	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/407,660	Lander et al
Examiner	**Art Unit**
Diana Johannsen	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 13, 2001*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-25, 27-36, 38, 40, and 42-49* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-25, 27-36, 38, 40, and 42-49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

FINAL ACTION

1. This action is in response to paper no. 7, filed March 13, 2001. Claims 26, 37, 39, and 41 have been canceled, and claims 1, 6, 8, 14, 19, 28, 33, 42, 44 and 46-49 have been amended. Claims 1-25, 27-36, 38, 40, and 42-49 are now pending. The amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The Declaration filed October 13, 2000, paper no. 5, has been entered.

4. The IDS filed March 13, 2001, paper no. 8, has been entered and considered. A copy of the signed PTO-1449 is included herewith.

Claim Rejections - 35 U.S.C. § 112

5. Claims 1-25, 27-36, 38, 40, and 42-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons stated below and in the Office action of paper no. 4.

Claims 1-25, 27 and 42-49 are indefinite over the recitation of the terms "identifying" and "identify" in claims 1, 14, 42, 44, and 46-48. The response traverses the rejection on the grounds

that "Applicants note that the Specification, page 15, lines 4-10, makes clear that the steps of the claimed methods can be carried out physically or virtually (i.e., without physical or actual manipulation, such as in a computer system)". This argument has been thoroughly considered but is not convincing. It is acknowledged that the specification does provide analysis "with computer software" as an example of virtual analysis, and state that "'virtually' is intended to mean without physical or actual manipulation". However, analysis "with computer software" does encompass methods requiring "physical or actual manipulation" (e.g., implementation in a computer by provision of data, commands for analysis of that data, etc.), whereas applicants definition of "virtually" excludes "physical or actual manipulation". Further, it is noted that the paragraph of the specification referenced by applicant states that "any of the steps of the methods described herein can be carried out physically or virtually". However, it is unclear as to how one could "obtain" or "treat" nucleic acid molecules "without physical or actual manipulation". Accordingly, the portion of the specification cited by applicant does not clarify whether the recitation of "identifying"/"identify" would in fact require any type of active step, or whether steps of "identifying" might encompass, e.g., thought processes. Accordingly, this rejection is maintained.

Claims 1-25, 27-36, 38, 40, 42-45 and 48-49 are indefinite over the recitation of the terms "analyzing" and "analyzed" in claims 1, 14, 28, 42, 44, and 48. The response traverses the on the grounds that "Applicants note that the Specification, page 15, lines 4-10, makes clear that the steps of the claimed methods can be carried out physically or virtually (i.e., without physical or

actual manipulation, such as in a computer system)". This argument has been thoroughly considered but is not convincing. It is acknowledged that the specification does provide analysis "with computer software" as an example of virtual analysis, and state that "'virtually' is intended to mean without physical or actual manipulation". However, analysis "with computer software" does encompass methods requiring "physical or actual manipulation" (e.g., implementation in a computer by provision of data, commands for analysis of that data, etc.), whereas applicants definition of "virtually" excludes "physical or actual manipulation". Further, it is noted that the paragraph of the specification referenced by applicant states that "any of the steps of the methods described herein can be carried out physically or virtually". However, it is unclear as to how one could "obtain" or "treat" nucleic acid molecules "without physical or actual manipulation". Accordingly, the portion of the specification cited by applicant does not clarify whether the recitation of "analyzing" and "analyzed" would in fact require any type of active step, or whether steps of "analyzing" might encompass, e.g., thought processes. Accordingly, this rejection is maintained.

Claims are indefinite over the recitation of the terms "selected" and "selecting" in claims 1, 12, 14, 24, 28, 31, and 46-48. The response traverses the on the grounds that "Applicants note that the Specification, page 15, lines 4-10, makes clear that the steps of the claimed methods can be carried out physically or virtually (i.e., without physical or actual manipulation, such as in a computer system)". This argument has been thoroughly considered but is not convincing. It is acknowledged that the specification does provide analysis "with computer software" as an

example of virtual analysis, and state that "'virtually' is intended to mean without physical or actual manipulation". However, analysis "with computer software" does encompass methods requiring "physical or actual manipulation" (e.g., implementation in a computer by provision of data, commands for analysis of that data, etc.), whereas applicants definition of "virtually" excludes "physical or actual manipulation". Further, it is noted that the paragraph of the specification referenced by applicant states that "any of the steps of the methods described herein can be carried out physically or virtually". However, it is unclear as to how one could "obtain" or "treat" nucleic acid molecules "without physical or actual manipulation". Accordingly, the portion of the specification cited by applicant does not clarify whether the recitation of "selected" and "selecting" would in fact require any type of active step, or whether steps of "selecting" might encompass, e.g., thought processes. Accordingly, this rejection is maintained.

Claims 42-45 are indefinite over the recitation of the limitation "proposed pairs" in claims 42 and 44. The response traverses the rejection on the grounds that the claims "have been amended to recite 'comparing the sequence of two fragments from the reduced representation'". However, this amendment does not clarify what might constitute the "proposed pairs" recited in step (d). Particularly, it is unclear as to what types of pairs might be considered to be "proposed" pairs, and as to how such pairs relate back to the "pairs of fragments" of claims 1 and 14. Accordingly, this rejection is maintained.

Claims 42-45 are indefinite over the recitation of the term "candidate single nucleotide polymorphisms" in claims 42 and 44. The response traverses the rejection on the following

grounds. The response states that "The function of the recited method step is to identify fragments which are truly orthologous (from the same chromosomal location) and to eliminate fragments which are not truly orthologous". The response states that "Sequence variations between sequences which are not orthologous are not true polymorphisms", and that "a 'candidate' polymorphism is a polymorphism which has not yet been validated as a true polymorphism". These arguments have been thoroughly considered but are not persuasive. It remains unclear as to how a "candidate single nucleotide polymorphism" would differ from a "single nucleotide polymorphism" within the context of the claimed invention. Further, would any sequence difference constitute a "candidate single nucleotide polymorphism", or would differences have to meet other criteria in order to constitute "candidates"? While applicants response further clarifies the intended purpose of the claimed invention, the types of differences that would be encompassed by the language "candidate single nucleotide polymorphism" remain unclear. Accordingly, this rejection is maintained.

Claims 42-45 are indefinite over the recitation of the phrase "determining the number of candidate matches for the same chromosomal location, wherein said candidate matches are accepted if said number of matches does not exceed expectations". First, it is acknowledged that claims 1 and 14 provide antecedent basis for the limitation "the same chromosomal location". With respect to the remainder of the rejection, the response traverses on the grounds that "Applicants believe that the phrase 'does not exceed expectations' is sufficiently clear when read in light of the Specification, particularly page 26, line 14, through page 27, line 14". This

argument has been thoroughly considered but is not convincing. While the portion of the specification referenced by applicant provides an example of how putative orthologues may be analyzed to determine whether a "candidate match" would constitute a "match", no particular limitations or definitions are provided that would provide a clear limitation on the recitation in the present claims of the language "if said number of matches does not exceed expectations". Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is further noted that the response does not address the rejection of the language "matches are accepted". Applicants arguments are not persuasive, and therefore this rejection is maintained.

Claims 43 and 45 are indefinite over the recitation of the phrase "wherein said expectations are determined according to binomial or Poisson distributions". It is acknowledged that, as argued in Applicants response, "Poisson distributions and binomial distributions are standard probability tools which are well within the knowledge of the skilled artisan". However, the present rejection was made because applicants claim language does not make clear how one is to employ "binomial or Poisson distributions" to determine expectations. While the response cites an example of the use of Poisson distributions in the specification, it is again noted that limitations from the specification are not read into the claims. Accordingly, this rejection is maintained.

Claim Rejections - 35 U.S.C. § 102

6. In view of the cancellation of claim 26, the rejection of the claim under 35 U.S.C. 102(b) as being clearly anticipated by Gu et al (BioTechniques 24(5):836-837 [5/1998]) is moot.

7. Claims 1-4, 8-10, 12-17, 21-22, 24-25, 27-29, 31-32, and 46-49 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Gu et al (BioTechniques 24(5):836-837 [5/1998]), for the reasons stated in the Office action of paper no. 4.

The response traverses the rejection on the following grounds. The response states that the claims "have been amended to recite the transitional phrase 'consisting essentially of' rather than 'comprising'". The response argues that Gu et al teach "that in their method the target sequence must be amplified with specific primers, requiring knowledge of the base composition of the target sequence to design PCR primers", whereas the claimed invention "does not require PCR or knowledge of the nucleic acid sequence". The response states that "as described in the Specification at page 22, lines 18-26, the 'nucleic acid-containing sample' can be the entire human genome, such as the genome derived from multiple individuals". The response argues that the present claims "as amended, do not recite that the nucleic acid-containing sample is subsequently amplified utilizing PCR, and in fact this is not a necessary element of the claimed method".

These arguments have been thoroughly considered but are not convincing for the following reasons. The claims as written remain sufficiently broad so as to encompass the methods of Gu et al. While it is acknowledged that the claims have been amended so as to recite the transitional language "consisting essentially of", the claims include a first step of "obtaining a

nucleic acid-containing sample". Such a step is sufficiently broad so as to encompass "obtaining" in any manner any type of "nucleic acid-containing sample". The step of obtaining amplification products taught by Gu et al constitutes a step of obtaining a "nucleic acid-containing sample" that is encompassed by the present claims. Further, with respect to applicants argument that the specification teaches that the "nucleic acid containing sample" may be "the entire human genome, such as the genome derived from multiple individuals", it is noted that no such limitation on the properties of the nucleic acid containing sample are recited in the claims. Additionally, no such limiting definition of "nucleic acid containing sample" is provided in the specification. Furthermore, the claims are not limited to samples of nucleic acids whose sequences are unknown. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Accordingly, applicants arguments are not persuasive.

Gu et al teach all the limitations recited in present claims 1-4, 8-10, 12-17, 21-22, 24-25, 27-29, 31-32, and 46-49, and therefore this rejection is maintained.

Claim Rejections - 35 U.S.C. § 103

8. Claims 6-7, 19-20, 36, 38, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al (BioTechniques 24(5):836-837 [5/1998]) in view of Landegren et al (Genome Res. 8(8):769-776 [8/1998]), for the reasons stated in the Office action of paper no. 4.

With respect to the Gu et al reference, the response traverses the rejection for the same reasons discussed in paragraph 7, above. Accordingly, the response to those arguments applies equally herein.

The response further traverses the rejection on the grounds that "Landegren et al. does not remedy the defects of Gu et al". The response states that "Landegren et al. state....that SNP analyses extend from investigation of small numbers of sequence variants known to be associated with a specific disease to investigations of markers across the genome", and that "Therefore, Landegren et al. suggest the use of known markers or known variants associated with disease and does not suggest identifying novel polymorphisms". The response concludes that Landegren et al "teach that all SNP-related methods require PCR amplification of known target sequences". The response further argues that a combination of the teachings of Gu et al and Landegren et al "would not provide a reasonable expectation of success in producing the claimed invention, as the teachings of Landegren et al. further support the disclosure of Gu et al. that PCR amplification is a necessary component of SNP discovery methods".

These arguments have been thoroughly considered but are not convincing for the following reasons. First, it is noted that the Landegren et al reference was cited for its teaching that SNPs may serve as markers of disease, not for a teaching of "known markers or known variants associated with disease". Further, it is noted that the present claims are not limited to methods in which only "novel polymorphisms" are "identified" and/or in which only samples of unknown nucleic acids are employed. Additionally, as discussed in paragraph 7, above, the claims

encompass "obtaining" in any manner any type of "nucleic acid-containing sample". Accordingly, methods in which "obtaining" is achieved by steps including amplification are encompassed by the present claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The combined references of Gu et al and Landegren et al suggest all the limitations of present claims 6-7, 19-20, 36, 38, and 40, and therefore this rejection is maintained.

9. Claims 5 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Wu et al (DNA 8(2):135-142 [1989]), for the reasons stated in the Office action of paper no. 4.

With respect to the Gu et al reference, the response traverses the rejection for the same reasons discussed in paragraph 7, above. Accordingly, the response to those arguments applies equally herein.

The response further traverses the rejection on the following grounds. The response states that "Wu et al. teach that *in situ* dot hybridization of DNA or RNA with an allele-specific oligonucleotide probe works equally well", and that "Wu et al. do not teach any method for identifying new polymorphisms by analysis of RNA, but rather teach the use of a known polymorphism-specific probe on a spot of total RNA isolated from an individual...to determine its presence or absence". The response argues the combination of Gu et al and Wu et al "would not provide a reasonable expectation of success in producing the claimed invention", as "Gu et al

teaches that in their methods the target sequence must be amplified with specific primers, requiring knowledge of the base composition of the target sequence".

These arguments have been thoroughly considered but are not convincing for the following reasons. First, it is noted that the Wu et al reference was cited for its teachings that identification of SNPs in RNA samples allows one to analyze the presence of mutations in mRNA, and that methods of SNP analysis may be "applied equally to DNA and RNA, making it possible to analyze the expression of polymorphic sequences", not for a teaching of allele specific hybridization or of "known" probes. Further, as discussed in paragraph 7, the present claims do not exclude the use of nucleic acids of known sequence, and the claims encompass "obtaining" in any manner any type of "nucleic acid-containing sample". Accordingly, methods in which "obtaining" is achieved by steps including amplification using "specific PCR primers" are encompassed by the present claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The combined references of Gu et al and Wu et al suggest all the limitations of present claims 5 and 18, and therefore this rejection is maintained.

10. Claims 11, 23, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Bonn et al (U.S. Patent No. 5, 585,236 [12/1996]), for the reasons stated in the Office action of paper no. 4.

With respect to the Gu et al reference, the response traverses the rejection for the same reasons discussed in paragraph 7, above. Accordingly, the response to those arguments applies equally herein.

The response further traverses the rejection on the following grounds. The response argues that "Bonn et al. states...that samples containing mixtures of nucleic acids may result from total synthesis of nucleic acids, cleavage of DNA or RNA with restriction endonucleases, as well as nucleic acid samples which have been multiplied and amplified using polymerase chain reaction techniques". The response further argues that the combined references "do not provide a reasonable expectation of success" because the combined references do not "in any way teach or suggest a method of identifying polymorphisms which does not require amplification of the target sequences".

These arguments have been thoroughly considered but are not convincing for the following reasons. First, it is noted that the Bonn et al reference was cited for its teachings of a particular method for separating nucleic acids, not for a teaching of different sources of nucleic acid samples. It is noted that the step further limited by the present claims is not the "obtaining" step, but the "selecting" step of (b)(ii). Further, as discussed in paragraph 7, above, the present claims encompass "obtaining" in any manner any type of "nucleic acid-containing sample". Accordingly, methods in which "obtaining" is achieved by steps including amplification using "specific PCR primers" are encompassed by the present claims. Although the claims are

interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The combined references of Gu et al and Bonn et al suggest all the limitations of present claims 11, 23, and 30, and therefore this rejection is maintained.

11. Claims 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Drmanac (U.S. Patent No. 6,025,136 [2/2000; effective filing date 12/1994]), for the reasons stated in the Office action of paper no. 4.

With respect to the Gu et al reference, the response traverses the rejection for the same reasons discussed in paragraph 7, above. Accordingly, the response to those arguments applies equally herein. The response further traverses the rejection on the grounds that the combined references of Gu et al and Drmanac et al "would not provide a reasonable expectation of success in producing the claimed invention" because the combined references do not "teach or suggest a method of identifying polymorphisms which does not require amplification of the target sequences". These arguments have been thoroughly considered but are not convincing. As discussed in paragraph 7, above, the present claims encompass "obtaining" in any manner any type of "nucleic acid-containing sample". Accordingly, methods in which "obtaining" is achieved by steps including amplification using "specific PCR primers" are encompassed by the present claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The combined references of Gu et al and Drmanac et al suggest all the limitations of present claims 33-35, and therefore this rejection is maintained.

12. In view of the cancellation of claims 37, 39, and 41, the rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Drmanac and Landegren et al is moot.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday from 7:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at 703/308-1152. The fax phone number for the Technology Center where this application or proceeding is assigned is 703/305-3014 or 305-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana Johannsen

July 26, 2001

CARLA J. MYERS
PRIMARY EXAMINER